To Each His Own

DEHP Yields Species-Specific Metabolic Phenotypes

Endocrine disruptors have been shown to disturb the balance between energy expenditure and storage in cellular models, a balance that is critical for proper metabolic functioning. Peroxisome proliferator–activated receptors (PPARs), potential molecular targets of endocrine disruptors in several tissues and organs, hold a key position as lipid sensors that direct metabolic gene expression. A new mouse study illustrates activation of a specific PPAR isotype with exposure to the endocrine disruptor diethylhexyl phthalate (DEHP) and provides evidence that the potential influence of DEHP exposure on diet-induced obesity may vary between species [***EHP* 118:234–241; Feige et al.**].

DEHP is a widely used industrial plasticizer that can leach from diverse consumer products including food packaging and medical devices such as plastic tubing and bags. When ingested, DEHP is converted to monoethylhexyl phthalate (MEHP), which is readily absorbed. Previous *in vitro* research has demonstrated that MEHP can activate all three PPAR isotypes (PPARα, PPARβ, and PPARγ). The result *in vivo* can be opposing effects depending on which isotype is activated: induction of adipogenesis (PPARγ) or fatty acid oxidation (PPARα, PPARβ).

To determine the physical and biochemical effects of DEHP exposure, weanling mice were fed regular diets, with treatment groups receiving either 100 mg DEHP/kg/day (low dose) or 1,000 mg DEHP/kg/day (high dose) in the chow. Food intake and physical activity did not differ between groups, and lean body mass was not affected. However, in DEHP-treated mice fat reserves were reduced, and blood tests indicated increased hepatic fatty acid oxidation. As a result, mice in the high-dose group gained 15% less weight than low-dose and control mice over the 10-week treatment period.

In a separate experiment, adult mice were fed a high-fat diet for 13 weeks. Fat mass increased from a baseline 8–10% of body mass to 30% in untreated mice but remained unchanged in mice receiving 500 mg DEHP/kg/day. Further experiments investigating the pattern of PPAR target gene expression and using mice lacking either PPARα or PPARβ revealed that DEHP effects were mediated through PPARα in the liver.

Finally, to make the model more applicable to humans, mice genetically engineered to carry human PPARα were exposed to DEHP. Interestingly, MEHP did not protect these mice from diet-related obesity as it did in wild-type mice; in fact, MEHP led to these mice being even more obese than controls. If this relationship holds true in humans, exposure to certain endocrine disruptors could potentially contribute to obesity by promoting fat accumulation.

Conclusions drawn from this study include the identification of hepatic PPARα as a key site for DEHP-associated disruption. The doses applied in this study are 2–3 orders of magnitude higher than estimated typical human exposures when normalized to body mass. However, the observation of subtle, species-specific differences in metabolic response to DEHP point to an important factor that should be considered as the biological effects of DEHP on human health are further explored.

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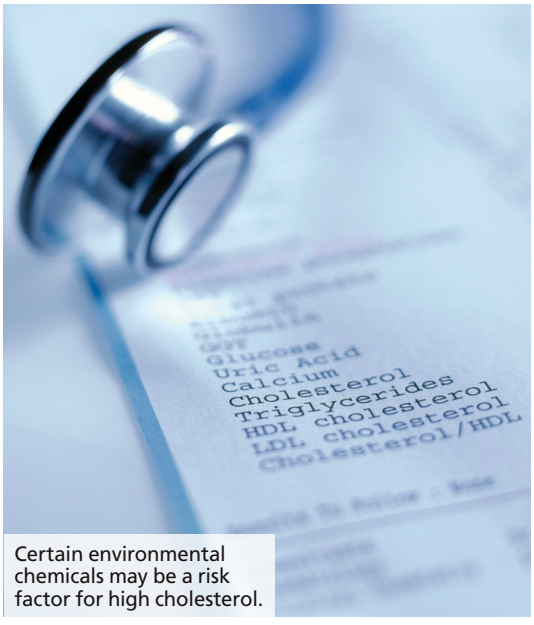
PFCs and Cholesterol

A Sticky Connection

Polyfluoroalkyl chemicals (PFCs), highly stable compounds used in consumer items such as food packaging, textiles, and paper products, are known to migrate throughout and persist in the environment. Animal studies have described the development of adverse health effects such as tumors and developmental delays with exposure to the PFCs perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). A new study now suggests these and other PFCs may affect serum cholesterol levels in humans [***EHP* 118:197–202; Nelson et al.**].

Elevated cholesterol levels are associated with an increased risk of cardiovascular disease, and are one of the conditions that define metabolic syndrome. Risk factors for high cholesterol include diet, low physical activity, and a family history of the condition, but increasing evidence indicates some environmental chemicals also may contribute. With estimated half-lives of up to 8.5 years, PFCs are classified as persistent organic pollutants (POPs). However, unlike most POPs, which are stored primarily in fat tissue, PFCs persist by forming chemical bonds to proteins in the liver and serum.

Previous studies in humans have reported positive associations between PFOS and PFOA exposures and higher cholesterol levels. The research team in the current study investigated the relationship between insulin resistance, cholesterol levels, body size, and exposure to two less studied PFCs, perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) in addition to PFOS and PFOA. The study used data from the 2003–2004 National Health and Nutrition Examination Survey.



Certain environmental chemicals may be a risk factor for high cholesterol.

The authors found a positive association between total cholesterol (TC) and serum concentrations of PFOS, PFOA, and PFNA. TC is the sum of low-density and very low-density lipoproteins ("bad" cholesterol) and high-density lipoproteins ("good" cholesterol). The findings appeared driven by an increase in the non–high-density lipoprotein fraction of TC, and the association was most pronounced for PFNA. In contrast, PFHxS concentrations were inversely related to TC: samples reflecting the highest PFHxS exposure had the lowest TC levels.

The authors observed little evidence of associations between body size, insulin resistance, and PFC concentrations. They note several limitations in this study, including the fact they could not rule out the possibility of reverse causality—that is, that having higher cholesterol levels could lead to increased PFC concentrations in the blood. Nevertheless, the results support previous epidemiologic research indicating that environmentally relevant exposures to PFCs may affect human cholesterol metabolism or homeostasis.

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